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*Original Article*

# Malignant Brenner tumor of the ovary: clinical, pathological and demographic analyses of 10 cases

Zhensong Yue[1], Tongguo Si[2], Zhanyu Pan[1], Wenfeng Cao[3], Zhuchen Yan[1], Zhansheng Jiang[1], Huaqiang Ouyang[1]

*Departments of [1]Integrated Chinese and Western Medicine, [2]Invasive Technology, [3]Pathology, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China*

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**Abstract:** Background: Brenner tumor is a rare ovarian tumor and mostly benign. Malignant Brenner tumor (MBT) is much rarer. Methods: The retrospective study was used to analyze the patients of MBT who were treated in our hospital from January 1979 to December 2011. The clinical, pathological and demographic characteristics of the patients were analyzed. Results: The median age of patients was 49.50 ± 11.30 years (ranging from 32 to 76 years). The initial symptom in the majority of patients was abdominal distension or abdominal pain (6/10, 60%). The mean size of the ovarian tumors was 16.43 ± 6.83 cm (ranging from 6.0 to 25.0 cm). Six patients (60%) were in Stage I, two patients (20%) were in Stage IIIC and two patients (20%) were in Stage IV. The cancer antigen-125 (CA125) levels decreased in patients receiving effective chemotherapy. The mean time of follow-up was 42.40 ± 31.81 months (ranging from 5 to 94 months). Five patients with either primary advanced tumor or recurrent tumor, developed distant metastasis: four patients had hepatic metastases, and one patient had cerebral and pulmonary metastases. Of the above five cases, four patients died of tumor and one patient died of cerebral hemorrhage. The rest five patients survived. Conclusion: The most significant factor affecting the prognosis of MBT is staging. Therefore, early diagnosis and treatment is the most effective method for prognosis improvement. Surgery remains to be the primary treatment for MBT and chemotherapy provides certain therapeutic effects as well. CA125 is a useful tumor marker for prognosis prediction and treatment efficacy monitoring.

**Keywords:** Brenner tumor, management, malignancy

## Introduction

Brenner tumor is a relatively rare tumor of ovary and accounts for only 1.7% of all ovarian tumors. Brenner tumor can be divided into three types including benign, borderline and malignant, and these three types can occur in patients at any age [1, 2]. Malignant Brenner tumor (MBT) is even rarer, and less than 100 cases of malignant Brenner tumor had been reported in the literature as of 2009 [3].

Brenner tumor usually presents no symptoms, especially when the tumor size is small. Therefore, the diagnosis of Brenner tumor in the majority of patients is an incidental pathological finding. In those symptomatic patients, the most common symptoms include abnormal vaginal bleeding, perceptible lumps and pain associated or not with the pelvic masses [4]. Brenner tumors are mostly unilateral [5]. Although serum level of CA125 is a useful tumor marker for MBT, the specific tumor marker for MBT has not been identified due to the rarity and variable histological criteria [2]. The immunohistochemical staining of MBT are often positive for urothelial specific protein 3, thrombomodulin and cytokeratin 7 and negative for cytokeratin 20. The primary treatment for MBT is surgery resection; the benefits and specific protocol of adjuvant chemotherapy have not been generally acknowledged [3].

In this study, we reported and analyzed the clinical, pathological and demographic characteristics of 10 cases of MBT.

## Materials and methods

We conducted a retrospective analysis on the patients diagnosed with MBT and treated in Tianjin Medical University Cancer Institute &

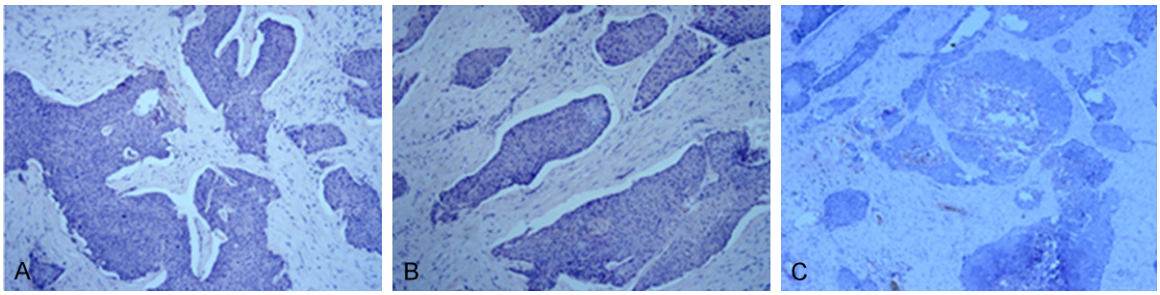


**Figure 1.** Malignant Brenner tumor of ovary. A: The tumor cells are shown a layer arrangement with obvious atypia and large deep stained nuclei. B: The tumor cells are distributed with various sizes of nest, and the shrunken fissure is seen between tumor and stroma. C: Multiple necrotic foci exist between the tumor nests. (Hematoxyline-eosin staining; original magnification, 40X).

Hospital from January 1979 to December 2011. Based on the review of imaging data, surgical records and pathologic slices of each patient (**Figure 1**), we adopted the 2010 FIGO staging system to perform a retrospective re-staging on each patient. The condition of each patient was evaluated on the basis of clinical follow-ups, level of tumor markers and imaging data. The clinical and pathological information included age, main symptoms, tumor size, surgical approach, histological type, disease stage, adjuvant therapy and time of recurrence and follow-up. The statistical analysis was completed with SPSS 16.0.

## Results

During a period of 32 years (from January 1979 to December 2011), ten patients were diagnosed with MBT (**Tables 1** and **2**). Among them, nine cases were diagnosed in the period from January 1993 to December 2011 and only one case before 1993. The median age of the patients was 49.50 ± 11.30 years (ranging from 32-76 years) and five patients (50%) were postmenopausal female. The clinical, pathological and demographic characteristics of 10 patients were listed in **Table 1**.

In view of the initial symptom, four patients first suffered from abdominal distension, two patients suffered from abdominal pain and three patients suffered from pelvic mass. One patient experienced initial symptom of hematuresis due to bladder invasion caused by tumor. Postmenopausal vaginal bleeding was seen in one patient with abdominal distension and one patient with pelvic mass.

The preoperative imaging examination or intraoperative observation found that three patients (30%) developed ascites (**Table 1**). Three patients did not have the record of tumor size since they were initially diagnosed in other hospitals. In the rest of seven patients, the mean size of ovarian tumor was 16.43 ± 6.83 cm (ranging from 6.0 to 25.0 cm). One patient (10%) developed bilateral ovarian tumor, four patients (40%) developed left ovarian tumor and five patients (50%) developed right ovarian tumor. Six patients (60%) were in Stage I (including one in Stage Ia, one in Stage Ib and four in Stage Ic), two patients (20%) were in Stage IIIc and another two patients (20%) were in Stage IV (one patient developed pulmonary and cerebral metastasis two months after surgery, and thus initially diagnosed as in Stage IV).

All the ten patients (100%) received surgery, including eight cases (80%) of complete hysterectomy, bilateral adnexectomy and greater omentum resection (simultaneous appendectomy in three cases and bladder-involved focus resection in one case) and two cases (20%) of exploratory laparotomy and biopsy. Nine patients (90%) received chemotherapy, including six cases of postoperative adjuvant chemotherapy and three cases of advanced palliative chemotherapy. The summary of chemotherapy was listed in **Table 2**. Among the six patients who received postoperative adjuvant chemotherapy, two patients experienced recurrence, including one case in Stage IIIC and one case in Stage IC. These two patients with recurrence underwent chemotherapy once again. The mean time of follow-up was 42.40 ± 31.81 months (ranging from 5 to 95 months). A total of five patients, including one patient with initial diagnosis of primary advanced stage IV and four patients with recurrent tumor, developed distant metastasis: four patients had hepatic

**Table 1.** Demographic, clinical and pathological characteristics of patients with ovarian MBT

| Patient No. | Age | Postmenopausal/ Ascites | Initial symptom | Tumor size/ side | Surgery | CA125 (IU/ml) | Stage | Chemotherapy | Recurrence/ interval to recurrence | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 51 | Yes/No | Abdominal pain | 25 cm/Right | Complete hysterectomy, bilateral adnexectomy, greater omentum resection and appendicectomy | 53.78 | Ic | Yes | No | 29 months/Survived |
| 2 | 56 | Yes/Yes | Abdominal distension | No data/Right | Complete hysterectomy, bilateral adnexectomy, greater omentum resection and appendicectomy | 143 | IIIc | Yes | Yes/13 months | 38 months/Died |
| 3 | 43 | No/Yes | Pelvic mass | 19 cm/Right | Exploratory laparotomy and right ovarian mass resection | 45.69 | IV | Yes | Yes/5 months | 10 months/Died |
| 4 | 55 | Yes/No | Abdominal pain | No data/Right | Complete hysterectomy, bilateral adnexectomy and greater omentum resection | 222.4 | Ic | Yes | Yes/22 months | 34 months/Died |
| 5 | 44 | Yes/No | Abdominal distension | 15 cm/Left | Complete hysterectomy, bilateral adnexectomy, greater omentum resection and appendicectomy | 16.07 | Ia | Yes | No | 61 months/Survived |
| 6 | 32 | No/No | Hematuresis | No data/Left | Complete hysterectomy, bilateral adnexectomy, greater omentum resection and bladder-involved focus resection | No data | IV | Yes | Not applicable | 5 month/Died |
| 7 | 46 | No/Yes | Abdominal distension | 11 cm/Right | Exploratory laparotomy and biopsy | 356.7 | IIIc | Yes | Yes/4 months | 14 months/Survived |
| 8 | 48 | No/No | Abdominal distension, vaginal bleeding | 24 cm/Left | Complete hysterectomy, bilateral adnexectomy, greater omentum resection | No data | Ic | Yes | No | 46 months/Survived |
| 9 | 47 | No/No | Pelvic mass | 6 cm; 6 cm/ Left and right | Complete hysterectomy, bilateral adnexectomy, greater omentum resection | No data | Ib | Yes | No | 93 months/Survived |
| 10 | 76 | Yes/No | Vaginal bleeding, pelvic mass | 15 cm/Left | Complete hysterectomy, bilateral adnexectomy, greater omentum resection | No data | Ic | No | No | 94 months/Died of cerebral hemorrhage |

**Table 2.** Summary of chemotherapy in patients with ovarian MBT

| Patient No. | Stage | Postoperative adjuvant chemotherapy | Advanced palliative chemotherapy | CA125 level in response to chemotherapy | Recurrence/ interval to recurrence | Additional chemotherapy for recurrence | CA125 level in response to additional chemotherapy | Follow-up |
|---|---|---|---|---|---|---|---|---|
| 1 | Ic | Taxol + Cisplatin ×2 | No | Reduced to normal | No | No | Not applicable | 29 months/survived |
| 2 | IIIc | Taxol + Cisplatin ×7 | No | Reduced to normal | Yes/13 months | Ifosfamide + Nedaplatin ×8 | Reduced to normal level | 38 months/died |
| 3 | IV | No | Cisplatin + Epirubicin ×2 | No data | Yes/5 months | Taxol + Cisplatin ×1 | No data | 10 months/died |
| 4 | Ic | Taxol + Oxaliplatin ×7; Gemcitabine + Nedaplatin ×4; Taxol + Carboplatin ×3; Pemetrexed + Cisplatin ×1 | No | Reduced first, but then increased indicating recurrence before it reduced to normal | Yes/22 months | Docetaxel + Lobaplatin ×4 | Increased | 34 months/died |
| 5 | Ia | Taxol + Cisplatin ×3 | No | Keep normal | No | No | Not applicable | 61 months/survived |
| 6 | IV | No | Cytoxan + Vincristine + Fluorouracil + BCNU ×1 | No data | Yes/5 months | No | No data | 5 months/died |
| 7 | IIIc | No | Taxol + DDP ×2 | Increased | Yes/4 months | DDP + Cytoxan + Fluorouracil ×3 | Reduced | 14 months/survived |
| 8 | Ia | Ifosfamide + Fluorouracil ×2 | No | No data | No | No | No data | 46 months/survived |
| 9 | Ib | CTX, VCR, 5-FU ×2 | No | No data | No | No | No data | 93 months/survived |
| 10 | Ia | No | No | No data | No | No | No data | 94 months/died of cerebral hemorrhage |

metastasis, and one patient had cerebral and pulmonary metastasis. Four of these five patients died of tumor and one patient died of cerebral hemorrhage. The rest five patients survived.

In the six patients who had tumor marker records, the preoperative level of CA125 was normal in one patient (16.7%) and high in five patients (83.3%) (Upper limit of CA125 is 35 U/ml). One patient received CA125 review within one week after surgery; the CA125 level increased to 53.78 U/ml and recovered to normal during the subsequent chemotherapy. In one patient with increased preoperative CA125, the CA125 level recovered to normal during the postoperative chemotherapy, but increased again after the relapse of tumor and reduced followed by effective chemotherapy; meanwhile, the patient had developed increased levels of human epididymis protein 4, carbohydrate antigen CA72-4 and human chorionic gonadotropin (HCG) as well. In one patient who had high level of postoperative CA125, the CA125 level continued to increase significantly six months later. Positron emission tomography (PET) indicated tumor recurrence in this patient eight months later. In addition to CA125, some patients developed increased levels of carbohydrate antigen 19-9, carbohydrate antigen 242 and CA724 as well as carcino-embryonic antigen (CEA).

## Discussions

The ovarian Brenner tumor is a rare type of adenofibroma. The origin of the Brenner tumor remains unknown. Currently, it is widely accepted that the Brenner tumor is originated from the surface epithelium of the ovary or the pelvic mesothelium through transitional cell metaplasia [6].

The clinical characteristics of 10 cases of MBT described in this study were generally consistent with previous reports [7, 8]. MBT occurs mainly during premenopausal or menopausal period. The patients in our study aged from 32 to 76 years (median age was 49.50 ± 11.30 years) and 5 (50%) of them were postmenopausal. The tumor size in the seven patients presented in this study ranged from 6-25 cm, which supported the conclusion that MBT is generally large (mean size 16-20 cm) as compared to the benign Brenner tumor. MBT mostly is unilateral and presents local dissemination and less than 50% of patients develop exterior pelvic metastasis [9]. In our study, only one patient had bilateral tumors and five (50%) patients, including one with initial diagnosis of advanced stage and four with recurrence, developed distant metastasis: four patients developed hepatic metastasis and one patient developed cerebral and pulmonary metastasis.

Ryback *et al* reported the mortality of MBT was approximately 55% and the mean survival time was 1 year [10]. The mortality in our study was 50%, which was consistent with the literature report. MBT confined to the ovary (stage I) had an excellent prognosis, with 5-year survival rate of 88% as reported by Austin et al [11]. The data presented here further supported this conclusion. In our study, among the six patients diagnosed as Stage I, five (83%) survived and one died of cerebral hemorrhage but not related to tumor. However, MBT patients with extra-ovarian spread behave similarly to other ovarian cancers. Interestingly, the prognosis of MBT in advanced-stage reported by Eichhornet always better than that of transitional cell carcinomas of ovary [12].

Currently, surgery is the primary therapeutic modality for MBT. Eight patients (80%) in the presented study received radical surgery treatment. The chemotherapy protocol specifically for MBT has not been established yet. The efficacy of postoperative adjuvant chemotherapy and/or radiotherapy still remains unclear [9, 13]. Recently, a retrospective study had shown the promising efficacy of anintensive systemic chemo therapy for the recurrent MBT [8]. Interestingly, CA125 levels had been widely used to monitor the efficacy of therapy. In our study, CA125 level decreased in response to effective chemotherapy and, increased accompanied with tumor recurrence, suggesting that CA125 is a useful tumor marker for disease progression and treatment efficacy monitoring.

In conclusion, we report the clinical and pathological characteristics of 10 cases of MBT in this study. We conclude that the most significant factor affecting the prognosis of MBT is staging. Therefore, early diagnosis and treatment is the most effective method for prognosis improvement. Surgery remains to be the

primary treatment for MBT and chemotherapy provides certain therapeutic effects as well. CA125 is a useful tumor marker for disease progression and treatment efficacy monitoring.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Zhensong Yue, Department of Integrated Chinese and Western Medicine, Tianjin Medical University Cancer Institute & Hospital, Huan-Hu-Xi Road, Ti-Yuan-Bei, He Xi District, Tianjin 300060, China. Tel: +86-22-23340123-1121; E-mail: zhensongyue@sina.cn

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